The Substitution Reaction of Pyrazine-2,3-dicarbonitrile Derivatives with Ammonia, Amines, Water and Alcohols

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5-Arylpyrazine-2,3-dicarbonitriles **1** and **2** give 2-alkylamino-5-arylpyrazine-3-carbonitriles **3** and **5** and 3-alkylamiono-5-arylpyrazine-2-carbonitriles **4** and **6** by the substitution reaction with amines but give only 3-aminopyrazine-2-carbonitrile derivative on the reaction with ammonia. The reaction of 5-arylpyrazine-2,3-dicarbonitriles (**1** and **2**) with alcohols in the presence of a base gives 2-alkoxypyrazine-3-carbonitrile derivatives **9** and **13** and 3-alkoxypyrazine-2-carbonitrile derivatives **10** and **14**. The reaction of water gives two pyrazinonecarbonitrile derivatives **11** and **12**. In these reactions the aryl groups on the pyrazine ring are 3,4-dimethoxyphenyl and benzo-15-crown-5.

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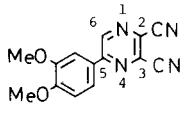
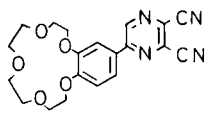
Pyrazinecarbonitrile derivatives having amino or alkoxy substituents have been known as precursors for the syntheses of biologically active compounds (1). Derivatives of 3-methoxypyrazine-2-carboxylic acid and 3-aminopyrazine-2-carboxylic acid are known to possess antimicrobial activity (2) and also used in the syntheses of compounds having diuretic or antineoplastic activities (3). However, a few direct syntheses of these compounds have been reported. Muehlmann and Day obtained 3-hydroxypyrazine-2-carboxamide by the treatment of ethanedial with 2-aminopropanediamide (4). Vogl and Taylor reported the syntheses of 3-aminopyrazine-2-carboxamides by the condensation of 1,2-dicarbonyl compounds with 2-amidino-2-aminoethanamide dihydrochloride (5,6). However, it seems difficult to prepare and to handle these propandiamide derivatives (7,8,9). Recently Otsuka, *et al.* developed the direct replacement of a nitrile group in a symmetrically substituted pyrazine-2,3-dicarbonitrile derivative, which was readily prepared from a 1,2-dicarbonyl compound and diaminomaleonitrile, with an alkoxide or alkylamine but the reaction gave the variety of products (10).

We have been studying the thermal and photochemical reactions of 5-(3,4-dimethoxyphenyl)pyrazine-2,3-dicarbonitrile (**1**) and 5-[(benzo-15-crown-5)-4′-yl]pyrazine-2,3-dicarbonitrile (**2**) (11,12). In the course of these studies we have been studying the nucleophilic substitution of these pyrazinedicarbonitrile derivatives. Pyrazinecarbonitrile derivatives having amino or alkoxy group and also crown ether moiety is a possible enzyme model which can associate a certain class of substrate molecule by the crown ether moiety. In this paper we wish to report the substitution reactions of the nitrile group in **1** and **2** with a primary amine or alcohol, and also with ammonia or water. The former substitution gave an alkylaminopyrazinecarbonitrile or an alkoxypyrazinecarbonitrile, and the latter substitution gave an aminopyrazinecarbonitrile or a pyrazinonecarbonitrile which are more versatile precursors for the syntheses of the compounds having pteridine moiety. We will also discuss the effect of the electron-donating substituent, dimethoxyphenyl or benzo-crown group, on the replacement of one of the two nitrile groups in **1** and **2**.



1



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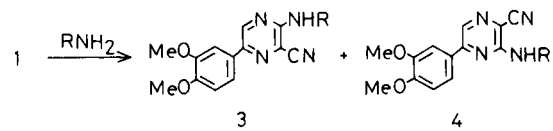
The syntheses of 5-(3,4-dimethoxyphenyl)pyrazine-2,3-dicarbonitrile (**1**) and 5-[(benzo-15-crown-5)-4′-yl]pyrazine-2,3-dicarbonitrile (**2**) have been reported in our recent paper (11).

Results and Discussion.

The Substitution of Nitrile Group by Amino Group.

The treatment of an ethanenitrile solution of **1** with an excess amount of butylamine or benzylamine gave the substitution product, 2-alkylamino-5-(3,4-dimethoxyphenyl)-pyrazine-3-carbonitrile (**3**) or 3-alkylamino-5-(3,4-dimeth-



3 4

3a, 4a : R = Bu 3b, 4b : R = CH_2Ph 3c, 4c : R = H

oxyphenyl)pyrazine-2-carbonitrile (**4**). The same treatment of **1** with excess amount ammonia by using a pressure bottle (3.5 atmospheres, 25°) gave 3-amino-5-(3,4-dimethoxyphenyl)pyrazine-2-carbonitrile (**4**, R = H) (Equation 1).

The products **3** and **4** were differentiated by ir and ^{1}H-nmr spectra. The ^{1}H-nmr signals of **3a** and **4a** at the lowest field are assignable to the hydrogen at C-6 position of the pyrazine ring (δ: **3a**, 8.59; **4a**, 8.30). The electron-

withdrawing nitrile group at the *para*-position lowered the chemical shift of C_6-H of **3a**, whereas the electron-donating butylamino group highered the chemical shift of the C_6-H of **4a**. In addition the ir spectrum of the nitrile

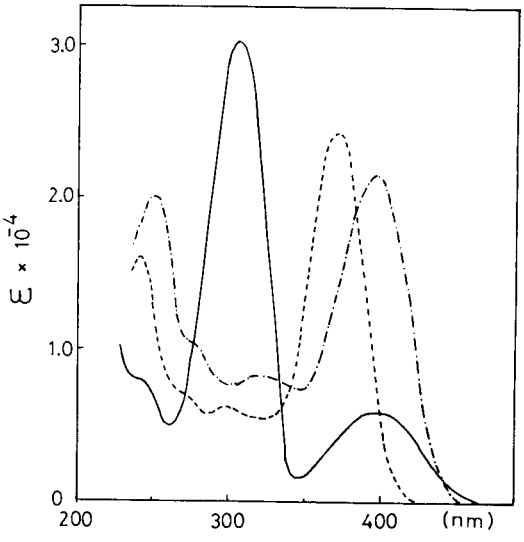


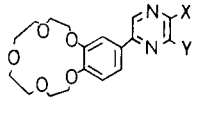
Figure 1. The uv-absorption of the substitution products by amines, **3a** (—), **4a** (----) and **4c** (—•—•), in ethanenitrile.

Table 1

Substitution Products from **1** and **2**

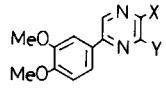
Starting material	Nucleophile	Product	Yield (%)	Spectral Data δ (a) (C_6-H)	Spectral Data ν (b) (cm^{-1})
1	$BuNH_2$	**3a**	35	8.59	2255
		4a	52	8.30	2230
1	$PhCH_2NH_2$	**3b**	17	8.96	2235
		4b	35	8.66	2230
1	NH_3	**4c**	58	8.40 (c)	2225 (d)
2	$BuNH_2$	**5**	36	8.32	—
		6	53	8.20	2235

(a) In deuteriochloroform. (b) In chloroform. (c) In DMSO-d_6. (d) In nujol mull.



5 : X = NHBu Y = CN

6 : X = CN Y = NHBu



7 : X = NHBu Y = $CONH_2$

8 : X = $CONH_2$ Y = NHBu

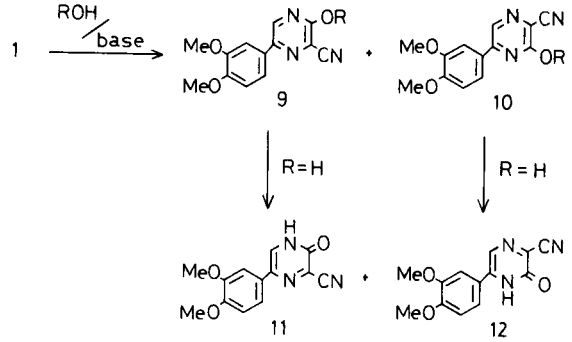
group in **3a** shows the weaker absorption band at 2255 cm^{-1}, whereas that of **4a** appears at 2230 cm^{-1}. The latter absorption band appears at the lower wave number due to the conjugation with the dimethoxyphenyl group at the *para*-position and is stronger than that of **3a** due to the polar nature of the nitrile group. The reaction of **1** with benzylamine gave the similar substitution products, **3b** and **4b**. In contrast to an alkylamine, ammonia gave only one substitution product, **4c**, in the reaction with **1**. The structure of **4c** was deduced from its ir (2225 cm^{-1}, CN) and uv spectra. The uv spectrum of **3a** is quite different from that of **4a**. The yields and spectral data of those products are summarized in Table 1 and Figure 1. The crown ether derivative **2** shows the same reactivity and the substitution reaction with butylamine takes place to give 5-[(benzo-15-crown-5)-4′-yl]-2-butylaminopyrazine-3-carbonitrile (**5**) and 5-[(benzo-15-crown-5)-4′-yl]-3-butylaminopyrazine-2-carbonitrile (**6**) in the ratio of 2:3 (total yield 89%).

The nitrile group in the substitution products **3** and **4** is easily hydrolyzed by the catalysis of alumina, and the retention of the products on alumina column for 24 hours gave the hydrolysis products **7** and **8**.

The Substitution of Nitrile Group by Alkoxy Group.

The substitution reaction took place also with alcohol or water in the presence of a base catalyst. The treatment of an ethanenitrile solution or a THF solution of **1** with alcohol contianing a base gave substitution products, 2-alkoxy-5-(3,4-dimethoxyphenyl)pyrazine-3-carbonitrile (**9**) and 3-alkoxy-5-(3,4-dimethoxyphenyl)pyrazine-2-carbonitrile (**10**) (Equation 2). The same treatment of **1** with aqueous alkali gave 5-(3,4-dimethoxyphenyl)-2(1*H*)-pyrazinone-3-carbonitrile (**11**) and 5-(3,4-dimethoxyphenyl)-3(4*H*)-pyrazinone-2-carbonitrile (**12**). These pyrazinones must be formed by the isomerization of the primary substitution product (**9c** and **10c**). The methylation of **11** and **12** loosed the ir absorptions at 1642 and 1663 cm^{-1} (ν, C=O) and gave **9a** and **10a** which were obtained by the direct substitution with methanol. The substitution products and spectral data are summarized in Table 2.

The structures of these alkoxy substitution products were determined from the spectral behaviors of the products though the effect of alkoxy group is not so prominent as that of amino group. The conjugation of the *para*-dimethoxyphenyl group shifts the ir absorption of the nitrile group on the pyrazine ring to the lower wave number and the *para*-alkoxy group pushes slightly the nmr



9a,10a : R = CH_3 9b,10b : R = CH_2Ph 9c,10c : R = H

Table 2

Substitution Products from **1** and **2**

Starting material	Nucleophile (base)	Product	Yield (%)	Spectral Data δ (a) (C_6-H)	Spectral Data ν (b) (cm^{-1})
1	MeOH	**9a**	37	8.71	2250
	(Na_2CO_3)	**10a**	42	8.66	2240
1	$PhCH_2OH$	**9b**	27	8.76	2245
	(NaH)	**10b**	34	8.70	2225
1	H_2O	**11**	15 (c)	—	—
	(NaOH)	**12**	50 (c)	—	—
2	MeOH	**13**	33 (d)	8.61	—
	(Et_3N)	**14**	49 (d)	8.56	2245

(a) In deuteriochloroform. (b) In chloroform. (c) Yields were obtained after methylation by diazomethane. (d) Products were not separated and the product ratio was determined by ^{1}H-nmr.

signal of C_6-H on the pyrazine ring to the higher field (see Table 2). The uv-spectra of **9a** and **10a** are different from each other and those spectra corrrespond to those of amino-substituted product of the same type (see Figure 2).

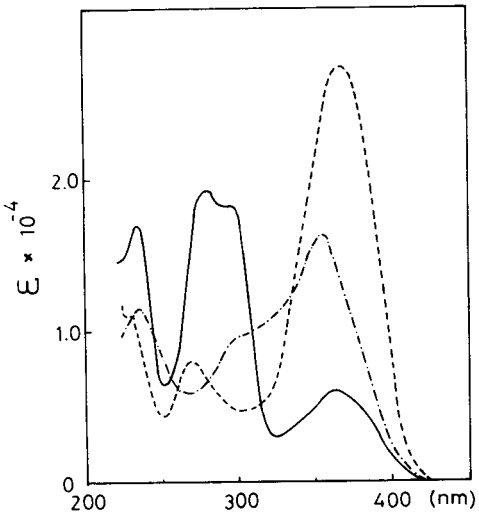
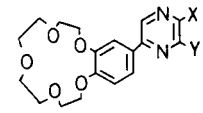
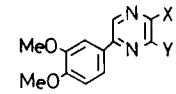


Figure 2. The uv-absorption of the substitution products by alcohols, **9a** (—), **10a** (----) and **18** (—•—•), in ethanenitrile.

The crown ether derivative **2** shows similar reactivity to give substitution products **13** and **14** with the methoxy group but the two isomers could not be separated.

Heating of the mixture of **11** and **12** in alkali caused the hydrolysis of the nitrile group to give the corresponding carboxylic acids (**15** and **16**) which gave ester **18** as an isolable product on methylation by diazomethane. The failure in isolation of the ester **17** is probably due to the instability of the intermediate acid **15** under the heated alkaline conditions. The hydrolysis of nitrile group in alkoxypyrazine derivatives **9** and **10** does not take place so easily as the hydrolysis of the nitrile group in aminopyrazine derivatives **3** and **4**. This difference in the ease of hydrolysis is ascribable to the internal base catalysis by the *ortho*-amino group in **3** and **4**.





13 : X = OMe Y = CN
14 : X = CN Y = OMe

15 : X = OH Y = CO_2H
16 : X = CO_2H Y = OH
17 : X = OMe Y = CO_2Me
18 : X = CO_2Me Y = OMe

Specific Features of the Substitution Reaction of Pyrazinedicarbonitriles.

In all trials in the present studies the substitution of nitrile group in pyrazine-dicarbonitrile derivatives **1** and **2** takes place preferentially at 3-position of 5-arylpyrazine-2,3-dicarbonitrile. This preference must be due to the increase of π-electron density, and hence less electrophilicity, at 2-position by the conjugation with an electron donating substituent, dimethoxyphenyl group.

Another feature is the lack of the addition of nucleophiles to the nitrile group under the present reaction conditions. This result is in sharp contrast to the study by Otsuka, *et al.* (10) in which the reaction in alcohol containing a base catalyst did not cause the clean substitution but gave imidates, addition products of alcohol to nitrile group. In the present study we used small portions of alcohol in an aprotic polar solvent and could exclude the addition reaction of alcohol to nitrile group.

The rather clean substitution reaction, though regiospecificity is not satisfactory, described in this paper offers a rather simple method for the preparation of alkoxy- or aminopyrazine derivatives, and must open a new way of the syntheses of pyrazine and pteridine derivatives of biological importance.

Another aspect of the present study is the substitution reaction of the pyrazinedicarbonitrile having a crown ether moiety, and this must add another variation in the syntheses of crown ether derivatives.

EXPERIMENTAL

The reaction of Pyrazine-2,3-dicarbonitriles with Amines and Ammonia.

2-Butylamino-5-(3,4-dimethoxyphenyl)pyrazine-3-carbonitrile (**3a**) and 3-butylamino-5-(3,4-dimethoxyphenyl)pyrazine-2-carbonitrile (**4a**).

A solution of 266 mg (1.0 mmole) of 5-(3,4-dimethoxyphenyl)pyrazine-2,3-dicarbonitrile (**1**) in 100 ml of dry ethanenitrile was added to 60 ml of freshly distilled butylamine and the mixture was allowed to stand for 5 hours at room temperature (20-25°). Evaporation of the solvent and the

amine under reduced pressure gave pale yellow solids which were passed through a short column of alumina (3 × 4 cm) with chloroform to remove the residual amine and other polar products. The products thus obtained were separated by a preparative tlc on alumina (chloroform-benzene, 1:1) to give **3a** (35%) and **4a** (52%). These were recrystallized from methanol for spectroscopic measurements. The product **3a** had mp 165°; ir (chloroform): 3431, 2859, 2255, 1581, 1502 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.59 (s, 1H), 7.35 (m, 2H), 6.85 (d, 1H, J = 8 Hz), 5.10 (diffused, NH), 3.90 (s, 3H), 3.85 (s, 3H), 3.34 (m, 2H), 1.80-1.15 (m, 4H), 0.90 (t, 3H, J = 6.5 Hz).

Anal. Calcd. for $C_{17}H_{20}N_4O_2$: C, 65.36; H, 6.45; N, 17.94. Found: C, 65.55; H, 6.40; N, 17.84.

The product **4a** has mp 137°; ir (chloroform): 3431, 2859, 2230, 1572, 1530, 1495 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.30 (s, 1H), 7.65 (d, 1H, J = 2 Hz), 7.50 (double d, 1H, J = 8 and 2 Hz), 6.85 (d, 1H, J = 8 Hz), 5.20 (diffused, NH), 3.90 (s, 3H), 3.85 (s, 3H), 3.59 (m, 2H), 2.10-1.45 (m, 4H), 0.90 (t, 3H, J = 6.5 Hz).

Anal. Calcd. for $C_{17}H_{20}N_4O_2$: C, 65.36; H, 6.45; N, 17.94. Found: C, 65.15; H, 6.38; N, 17.90.

5-[(Benzo-15-crown-5)-4′-yl]-2-butylaminopyrazine-3-carbonitrile (**5**) and 5-[(Benzo-15-crown-5)-4′-yl]-3-butylaminopyrazine-2-carbonitrile (**6**).

A solution of 396 mg (1.0 mmole) of 5-[(benzo-15-crown-5)-4′-yl]pyrazine-2,3-dicarbonitrile (**2**) in 80 ml of dry ethanenitrile was treated with 20 ml of freshly distilled butylamine and the mixture was allowed to stand for 16 hours at room temperature. The same work-up as mentioned above but using chloroform-methanol (99:1) as an eluent gave the crystals of products mixture of **5** and **6** (2:3) in 89% yield. A preparative tlc could not separate the mixture. Spectroscopic data of the mixture are as follows: ir (nujol): 3455, 3348, 2235, 1632, 1570, 1507 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.32 and 8.20 (s, total 1H), 7.65 (diffused, 2H), 6.85 (diffused, 1H), 5.35 (broad, NH), 4.15 (broad s, 4H), 3.89 (broad, 4H), 3.72 (broad, 8H), 3.51 (m, 2H), 1.82-1.22 (m, 4H), 0.99 (t, 3H, J = 6.5 Hz).

Anal. Calcd. for $C_{23}H_{30}N_4O_5$: C, 62.42; H, 6.83; N, 12.66. Found: C, 62.28; H, 6.78; N, 12.44.

2-Benzylamino-5-(3,4-dimethoxyphenyl)pyrazine-3-carbonitrile (**3b**) and 3-Benzylamino-5-(3,4-dimethoxyphenyl)pyrazine-2-carbonitrile (**4b**).

A solution of 266 mg (1.0 mmole) of **1** in 50 ml of dry ethanenitrile was treated with 5 ml of freshly distilled benzylamine and the mixture was allowed to stand for 20 hours at room temperature. The same work-up procedure as the case of butylamine gave **3b** (17%) and **4b** (35%). The product **3b** had mp 197-198°; ir (chloroform): 3500, 3385, 2845, 2235, 1639, 1580, 1501 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.96 (s, 1H), 7.60 (m, 7H), 7.14 (d, 1H, J = 8 Hz), 5.79 (diffused, NH), 4.77 (d, 2H, J = 6 Hz), 4.09 (s, 3H), 4.02 (s, 3H).

Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.18. Found: C, 69.13; H, 5.19; N, 15.91.

The product **4b** had mp 207-208°; ir (chloroform): 3505, 3395, 2845, 2230, 1639, 1575 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.66 (s, 1H), 7.85 (m, 2H), 7.60 (m, 5H), 7.19 (d, 1H, J = 8 Hz), 5.90 (diffused, NH), 4.96 (d, 2H, J = 6 Hz), 4.08 (s, 3H), 4.02 (s, 3H).

Anal. Calcd. for $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24; N, 16.18. Found: C, 69.62; H, 5.35; N, 15.93.

3-Amino-5-(3,4-dimethoxyphenyl)pyrazine-2-carbonitrile (**4c**).

A suspension of 266 mg (1.0 mmole) of **1** in 30 ml of ethanenitrile was placed in a pressure bottle (a medium pressure glass autoclave) and bubbled with gaseous ammonia for 30 minutes at -40°. The mixture became homogeneous at the end of bubbling and the sealed reaction bottle showed 3.5 atmospheres on warming to room temperature. After standing for 48 hours, the mixture was condensed under reduced pressure to give crude solids. Chromatography of the residue on alumina (2 × 10 cm) eluted by chloroform gave the yellow crystal of **4c** (58%). The product was recrystallized from methanol for spectroscopic measurements. The product **4c** has mp 206-207°; ir (nujol): 3425, 3345, 2225, 1641, 1518 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.40 (s, 1H), 7.61 (m, 2H), 6.93 (m, 3H), 3.90 (s, 6H).

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.98; H, 4.72; N, 21.87. Found: C, 60.67; H, 4.59; N, 21.54.

The Reaction of Pyrazinedicarbonitrile Derivatives with Alcohols and Water.

2-Methoxy-5-(3,4-dimethoxyphenyl)pyrazine-3-carbonitrile (**9a**) and 3-Methoxy-(3,4-dimethoxyphenyl)pyrazine-2-carbonitrile (**10a**).

A mixture of 266 mg (1.0 mmole) of 5-(3,4-dimethoxyphenyl)pyrazine-2,3-dicarbonitrile (**1**), 10 ml of methanol and excess sodium carbonate in 60 ml of ethanenitrile was stirred for 30 hours at room temperature. After slow addition of 4 ml of 10*N* hydrochloric acid, the mixture was condensed under reduced pressure and the residue was dissolved in chloroform (2 × 30 ml). The combined chloroform solution was condensed after washing with water (2 × 15 ml) and drying over sodium sulfate, and pale yellow solids of products **9a** and **10a** were obtained. The two isomers were separated by preparative tlc on alumina (chloroform-benzene, 1:1) to afford **9a** (37%) and **10a** (42%). These were recrystallized from methanol for spectroscopic measurements. The product **9a** had mp 163°; ir (chloroform): 2845, 2250, 1615, 1518 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.71 (s, 1H), 7.51 (m, 2H), 7.00 (d, 1H, J = 8 Hz), 4.10 (s, 3H), 3.96 (s, 3H), 3.89 (s, 3H).

Anal. Calcd. for $C_{14}H_{13}N_3O_3$: C, 61.98; H, 4.83; N, 15.49. Found: C, 62.25; H, 4.68; N, 15.72.

The product **10a** had mp 212°; ir (chloroform): 2850, 2240, 1603, 1523 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.66 (s, 1H), 7.69 (m, 2H), 6.99 (d, 1H, J = 8 Hz), 4.19 (s, 3H), 3.99 (s, 3H), 3.95 (s, 3H).

Anal. Calcd. for $C_{14}H_{13}N_3O_3$: C, 61.98; H, 4.83; N, 15.49. Found: C, 61.61; H, 4.55; N, 15.54.

5-[(Benzo-15-crown-5)-4′-yl]-2-methoxypyrazine-3-carbonitrile (**13**) and 5-[(Benzo-15-crown-5)-4′-yl]-3-methoxypyrazine-2-carbonitrile (**14**).

A mixture of 396 mg (1.0 mmole) of 5-[(benzo-15-crown-5)-4′-yl]pyrazine-2,3-dicarbonitrile (**2**), 2 ml of methanol, 2 ml of triethylamine in 50 ml of ethanenitrile was allowed to stand for 30 hours at room temperature. After condensation of the mixture under reduced pressure, the residue was passed through a short column of alumina (3 × 5 cm) with chloroform to afford a 2:3 mixture of **13** and **14** (total 82%). These products could not be separated by a preparative tlc. Spectroscopic data of the mixture are as follows: ir (nujol): 2245, 1602, 1508 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.61 and 8.56 (s, total 1H), 7.62 (m, 2H), 6.91 (m, 1H), 4.29 (m, 4H), 4.14 and 4.08 (s, total 3H), 3.94 (m, 4H), 3.74 (s, 8H).

Anal. Calcd. for $C_{20}H_{23}N_3O_6$: C, 59.84; H, 5.78; N, 10.47. Found: C, 60.16; H, 5.86; N, 10.18.

2-Benzyloxy-5-(3,4-dimethoxyphenyl)pyrazine-3-carbonitrile (**9b**) and 3-Benzyloxy-5-(3,4-dimethoxyphenyl)pyrazine-2-carbonitrile (**10b**).

Sodium hydride (200 mg, 50% dispersion in mineral oil) was added to the solution of 266 mg (1.0 mmole) of **1** and 2 ml of benzyl alcohol in 90 ml of dry tetrahydrofuran, and the mixture was allowed to stand for 24 hours at room temperature. After the addition of 1 ml of acetic acid, the reaction mixture was condensed under reduced pressure and the residue was dissolved in 30 ml of chloroform. The exactly same purification procedure as described for the methoxy derivatives **9a** and **10a** gave the benzyloxy-substitution products **9b** and **10b** in 27 and 34% respectively.

The product **9b** had mp 179°; ir (chloroform): 2849, 2245, 1602, 1521 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.76 (s, 1H), 7.61-7.42 (m, 7H), 7.01 (d, 1H, J = 8 Hz), 5.59 (s, 2H), 4.01 (s, 3H), 3.39 (s, 3H).

Anal. Calcd. for $C_{20}H_{17}N_4O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.02; H, 4.87; N, 12.43.

The product **10b** had mp 212°, ir (chloroform): 2949, 2225, 1602, 1523 cm^{-1}; ^1H-nmr (deuteriochloroform): δ 8.70 (s, 1H), 7.62-7.29 (m, 7H), 7.00 (d, 1H, J = 8 Hz), 5.56 (s, 2H), 4.01 (s, 6H).

Anal. Calcd. for $C_{20}H_{17}N_4O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.04; H, 4.88; N, 12.16.

5-(3,4-Dimethoxyphenyl)-2(1*H*)-pyrazinone-3-carbonitrile (**11**) and 5-(3,4-Dimethoxyphenyl)-3(4*H*)-pyrazinone-2-carbonitrile (**12**).

A mixture of 266 mg (1.0 mmole) of **1** and 10 ml of 1*N* aqueous sodium hydroxide in 60 ml of ethanenitrile was allowed to stand for 30 hours at room temperature. The addition of 4 ml of concentrated hydrochloric acid changed the color of the mixture from yellow to orange. Orange solids were obtained by the condensation of the reaction mixture, the addition of 10 ml of water, and filtration. The solids thus obtained were washed with hot water and methanol to afford the mixture of pyrazinones **11** and **12** (total 220 mg). The two isomers were not separated by a preparative tlc. The mixture suspended in 10 ml of methanol was treated with an ethereal solution of diazomethane until the mixture became homogeneous solution. The methylated products were separated by a preparative tlc to give **9a** and **10a** in 15 and 50% yield, respectively.

Hydrolyses of the Substitution Products.

5-(3,4-Dimethoxyphenyl)butylaminopyrazine-3-carboxamide (**7**) and 5-(3,4-Dimethoxyphenyl)-3-butylaminopyrazine-2-carboxamide (**8**).

A chloroform solution (5 ml) of 52 mg of the butylamino derivative, 2-butylamino-5-(3,4-dimethoxyphenyl)pyrazine-3-carbonitrile (**3a**) or 3-butylamino-5-(3,4-dimethoxyphenyl)pyrazine-2-carbonitrile (**4a**), was adsorbed on 10 g of alumina and allowed to stand for 24 hours at room temperature. Elution of the product with chloroform from the alumina column gave the hydrolysis products, **7** or **8**, in quantitative yield. Those products were recrystallized from benzene-methanol for spectroscopic measurements. The product **7** had mp 138°; ir (chloroform): 3512, 3381, 3318, 2859, 1667, 1591, 1501 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.60 (broad, NH_2), 8.30 (s, 1H), 7.40 (double d, 1H, J = 8 and 2 Hz), 7.30 (d, 1H, J = 2 Hz), 6.80 (d, 1H, J = 8 Hz), 5.00 (broad, NH), 3.90 (s, 3H), 3.85 (s, 3H), 3.50 (m, 2H), 1.80-1.15 (m, 4H), 0.90 (t, 3H, J = 6.5 Hz).

Anal. Calcd. for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96. Found: C, 61.58; H, 6.78; N, 17.36.

The product **8** had mp 142°; ir (chloroform): 3513, 3381, 3318, 2859, 1662, 1583, 1554, 1492 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 8.40 (broad, NH_2), 8.15 (s, 1H), 7.50 (double d, 1H, J = 8 and 2 Hz), 7.40 (d, 1H, J = 2 Hz), 6.85 (d, 1H, J = 8 Hz), 5.10 (broad, NH), 3.90 (s, 3H), 3.85 (s, 3H), 3.59 (m, 2H), 2.10-1.45 (m, 4H), 0.90 (t, 3H, J = 6.5 Hz).

Anal. Calcd. for $C_{17}H_{22}N_4O_3$: C, 61.80; H, 6.71; N, 16.96. Found: C, 62.08; H, 6.93; N, 17.39.

Methyl 5-(3,4-Dimethoxyphenyl)-3-methoxypyrazine-2-carboxylate.

A suspension of 100 mg of crude pyrazinones, 5-(3,4-dimethoxyphenyl)-2(1*H*)-pyrazinone-3-carbonitrile (**11**) and 5-(3,4-dimethoxyphenyl)-3(4*H*)-pyrazinone-2-carbonitrile (**12**), in 10 ml of 5*N* aqueous sodium hydroxide was heated to 60° for 5 hours. The addition of concentrated hydrochloric acid after cooling precipitated out red solids which were collected by filtration. A suspension of the solids in 10 ml of methanol was treated with an ethereal solution of diazomethane until the solids disappeared. Condensation of the solution and chromatography of the residue on alumina (2 × 5 cm) gave 60 mg of methyl 5-(3,4-dimethoxyphenyl)-3-methoxypyrazine-2-carboxylate which had mp 138-139°; ir (chloroform): 2845, 1728, 1601, 1516 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 9.39 (s, 1H), 7.40 (m, 2H), 7.18 (d, 1H, J = 8 Hz), 4.16 (s, 3H), 4.13 (s, 3H), 4.08 (s, 3H), 4.05 (s, 3H).

Anal. Calcd. for $C_{15}H_{16}N_2O_5$: C, 57.34; H, 4.87; N, 8.47. Found: C, 57.64; H, 4.98; N, 8.41.

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